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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,410	07/10/2001	Dan E. Robertson	DIVER1180-2	8980

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 01/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,410	ROBERTSON ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *42-55,61-63,65 and 88-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,16,20-23,40,41,67,68,80-82,98-102,107-111,113-117 and 126* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 6-15, 17-19, 24-39, 56-60, 64, 66, 69-79, 83-87, 93-97, 103-106, 112 and 118-125 have been canceled. Claims 1-5, 16, 20-23, 40-55, 61-63, 65, 67, 68, 80-82, 88-92, 98-102, 107-111, 113-117 and newly presented claim 126 are still at issue and are present for examination.

Applicants' arguments filed on 11/3/05, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 42-55, 61-63, 65 and 88-92 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the response filed 6/2/03. Claims 1-5, 16-18, 20-23, 40-41, 67, 68, 77, 78, 80-82, 85, 97-102, 107-109 and newly presented claims 110-125 are examined herein.

The benefit claim filed on 5/17/04 was not entered because the required reference was not timely filed within the time period set forth in 37 CFR 1.78(a)(2) or (a)(5). If the application is an application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the reference to the prior application

must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a nonprovisional application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the reference to the prior application must be made during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). Applicant previously filed a petition for an unintentionally delayed benefit claim under 37 CFR 1.78(a)(3) or (a)(6). The petition was denied on 5/28/04. As such the benefit claim remains improper and has not been entered. A renewed petition under 37 CFR 1.78(a)(3) or (a)(6) is necessary for the instant application to obtain the benefit of PCT/US07/02039. See the petition decision of 5/28/04.

Claim 20 is objected to because of the following informalities: "has a 95% sequence identity" is presumed to be "has at least 95% sequence identity". Appropriate correction is required.

Claim 107 is objected to because of the following informalities: the phrase "comprises catalysis of hydrolyzing ester groups to organic acids and alcohols" is awkward. "comprises catalyzing the hydrolysis of an ester to an organic acid and an alcohol" is suggested. Appropriate correction is required.

Claims 16, 67, 68, 80, 81, 107-111, 113-117 and 126 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16 and 67 (upon which claims 68, 80, 81, 110, 111, and 113-117 depend) are indefinite in the recitation of "can specifically hybridize to an esterase-encoding sequence" as it is unclear to what sequence the claimed nucleic acid must specifically hybridize. There are infinite number of possible esterase encoding sequences such that there is no way to even determine if a nucleic acid can specifically hybridize to an infinite number of sequences. Furthermore, the use of the term "specifically hybridize" with a genus of nucleic acids is unclear as the term "specifically" in the art means that the sequence hybridizes to the reference sequence but not to other sequences. As such any nucleic acid which can specifically

hybridize to one nucleic acid by definition cannot hybridize to others with different sequences, even where both are members of a single genus.

Claims 107-109 are unclear in the recitation of "nucleic acid of claim 1 or claim 3, wherein the esterase activity…" as the nucleic acid of claim 3 is not required to encode a protein having esterase activity. Claim 126 is similarly unclear in the recitation of "nucleic acid of claim 1 or claim 3, wherein the polypeptide retains esterase activity…".

Claim 108 is indefinite in the recitation of "wherein the esterase activity comprises hydrolase activity" as an esterase is by definition an enzyme with hydrolase activity, i.e., the ability to catalyze the hydrolysis of an ester bond. As such the claim is not further limiting of claim 1 or 3.

Claims 1, 3-5, 16, 20-23, 40, 41, 67, 68, 80-82, 98-102, 107-111, 113-117 and 126 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is explained in the previous Office Action.

As previously discussed, Claims 1 and 22 are directed to polynucleotides having 90% sequence identity to SEQ ID NO:26 and encoding a polypeptide with an esterase activity or polynucleotides encoding a protein having 90% sequence identity to SEQ ID NO:36 while claims 20 and 21 as amended to be dependent from claim 1 are directed to polynucleotides having 95% (and 97%) sequence identity to SEQ ID NO:26 and encoding a polypeptide with an esterase activity. Previously Claims 40 and 107-109 were limited to vectors and host cells comprising said nucleic acids or methods of expressing said nucleic acids however, these claims have been amended to depend from Claim 3 as well as claim 1 and thus are no longer so limited. Applicants argue the written description rejection as it was applied to these claims by arguing that one skilled in the art would have understood the meaning and scope of the term esterase activity, which includes the hydrolysis or synthesis of an ester. However, this was never an issue. If the meaning of the term esterase was unclear, a rejection under 35 U.S.C. 112, second paragraph would have been made. The scope of the term is clear, but is enormously broad such that the disclosed species are clearly not representative of the genus claimed. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied

through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The claimed genus is enormously variable in functional characteristics in view of the broad scope of the term esterase. All members of the genus will not catalyze the same reaction. Yet the specification describes completely only the nucleic acid of SEQ ID NO:26 which encodes the esterase of SEQ ID NO:36. This single species is not representative of all members of the genus. The Office never required as applicants imply that the specification must completely define the substrate specificity of all members of the genus completely. What the Office did require is that the claim be limited to a genus for which the disclosed specie(s) is

representative of the structure and function of all members of the genus. This is clearly not the case here.

The remainder of the claims recite even broader genera of nucleic acids than recited in Claims 1 and 20-22. As such all discussion of Claims 1 and 20-22 applies to these claims as well. However, these claims further include fragments and variants of the nucleic acids of Claims 1 and 20-22 which completely lack any disclosed functional limitation at all. Applicants statements that they believe the instant amendments address this issue is not persuasive. These claims remain without any functional limitations at all. Applicants argue that that describing a genus of polynucleotides in terms of physico-chemical properties (e.g., a % sequence identity or stringent hybridization to an exemplary nucleic acid or polypeptide, e.g., SEQ ID NO:26 or 36) and function (e.g., encoding a polypeptide having esterase activity) satisfies the written description requirement of section 112, first paragraph. First, it should be noted that the above discussion with regard to "esterase activity" of claims 1 and 20-22 clearly applies here as well, however, even if the recited activity was sufficiently limited (for example having the ability to hydrolyze one or more of the esters in the short-chain or long chain ester mixtures disclosed in the specification),

applicants arguments are not relevant because the instant claims are not so limited.

Claims 1, 3-5, 16, 20-23, 40, 41, 67, 68, 80-82, 98-102, 107-111, 113-117 and 126 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding SEQ ID NO:36, does not reasonably provide enablement for any polynucleotide having at least 90-97% sequence identity to SEQ ID NO:26 and encoding a polypeptide with any esterase activity, or any polynucleotide which will hybridize of SEQ ID NO:26 under defined conditions or any polynucleotide comprising at least 30 bases of a sequence having 90% identity to SEQ ID NO:26 and encoding a polypeptide having esterase activity, or any polynucleotide comprising a fragment of SEQ ID NO:26 or encoding fragments of SEQ ID NO:36, or all fragments and variants thereof or vectors and host cells comprising said nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is explained in the previous Office Action.

Applicant note that one of the Office's concerns regards the scope of the invention and the size of the claimed genus and states that the instant amendment addresses this issue by

amending Claims 3-5 to encompass isolated or recombinant nucleic acids that hybridize to a nucleic acid comprising a sequence as set forth in SEQ ID NO:26, and encoding a polypeptide having an esterase activity. However, Claims 3-5 are not in fact limited as argued by applicants. Claims 3-5 each recite any nucleic acid which hybridizes to a sequence having esterase activity (i.e., SEQ ID NO:26) under specific conditions (different in each of Claims 3-5). The claimed nucleic acid does not have to encode an esterase. The ability of a nucleic acid to hybridize to another in no way defines its function. Hybridization is a structurally defined characteristic such that limitations which recite hybridization define the structure of the claimed nucleic acid only. If applicants wish claims 3-5 to recite nucleic acids which encode an esterase the following language is suggested: "An isolated nucleic acid encoding a polypeptide having esterase activity, wherein said nucleic acid hybridizes to the nucleic acid of SEQ ID NO:26 or its complete complement under conditions …"

Applicants argue that the teachings of Guo et al., previously cited by the Office are insufficient to rebut the presumptively enabled specification and therefore cannot support a *prima facie* case of lack of enablement. Applicants argue that while Guo's model does predict that random codon replacement

will generate many inactive variants, Guo et al. in fact, found 920 tolerated or active variants and thus, Guo actually demonstrates that significant numbers of active variants can be generated using a random mutation and screening protocol. However, this is not well taken as Guo et al. were making and testing variants having only from 1-11 substitutions within a 298 amino acid long protein (i.e., having from 96.3-99.6% identity to the wild type protein) and a **specific** enzymatic activity. Applicants claims are not so limited in either structure or function. Claims limited in scope to a genus nucleic acids encoding proteins having similar identities to those of Guo et al. and a specific function which could be assayed would likely not have been rejected. However, no such claims are present in the instant case. While the previous rejection only clearly stated that nucleic acids encoding SEQ ID NO:36 would be enabled while the rejected claims were not commensurate in scope with the enablement without defining exactly what sub-genus in between might be acceptable, the rejection does not state that such a subgenus would not be allowable. However, it is not the examiners job to define for applicants the exact scope that they should claim in order provide them the broadest possible coverage that would be enabled when no claims are presented reciting such intermediate

possibilities. The narrowest of applicants claims that are rejected are those of Claims 1 and 20-22. Claim 1 was specifically addressed in the previous Office Action which clearly explained why randomly making variants having only 90% identity to SEQ ID NO:26 and testing them for those retaining activity would be undue experimentation based on a numerical estimate of what percentage of such randomly constructed mutants would be active. It is well accepted in the art (and the data of Guo et al. shows experimentally) that tolerance to modification for a given protein diminishes in an exponential fashion with each further and additional modification while the numbers of possible variants increases exponentially. As such what appear to be fairly small changes in the %identity to a specific sequence recited in a claim may well make large changes in the amount of experimentation necessary as well as the expectation of success such that the determination of whether it would require undue experimentation to make and use the full scope of what is claimed can be very different. Absent limitations to the scope of the claims such that randomly making variants and testing them for those retaining activity would not be undue experimentation, guidance regarding (A) regions of the protein structure which may be modified without effecting esterase activity; (B) the general tolerance of esterases to

modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) guidance as to which of the essentially enormous number of possible choices is likely to be successful is clearly necessary and is not provided by the instant specification. It is noted that current claims 20 and 21 (which are now amended to depend from claim 1) and 22 are included in the instant rejection despite the structural limitation to a genus for which randomly making variants and testing them for those retaining activity would arguably (for Claim 20) and clearly (for Claims 21 and 22) not be undue experimentation based on an similar analysis using the numerical estimates of Guo et al. because the functional limitation (i.e., esterase activity) of these claims is so broad as to require screening all variants for not just one particular activity (as did Guo et al.) but to require they be screened for hundreds of distinct activities each. This would clearly still be undue experimentation. Limitation of these claims to a specific esterase activity to be screened for would overcome this rejection for claims 20-22.

Applicants argue that nevertheless, while not necessary, if one skilled in the art desired some structural guidance as to what amino acid substitutions could be made to make the genus of

esterase-encoding nucleic acids of the invention, such guidance could be found both in the specification and the state of the art at the time of the invention. For example, the specification provides express guidance regarding what amino acid substitutions could be made to make the genus of esterase encoding nucleic acids of the invention be in paragraphs [54] or [205] of the specification; and the prior art provides teachings regarding for example, active sites and structures of various polypeptides having esterase activity. However, this is not persuasive because the guidance provided in the specification is so general in nature as to add little or nothing to the predictability of which variants should be made and while the art provides teachings with regard to active sites and structures of various polypeptides having esterase activity, the relevance of these to variants of SEQ ID NO:26 is highly questionable indeed as the protein encoded by the single disclosed species (i.e., SEQ ID NO:36) has little or no structural identity to the esterases discussed in the prior art. If such structural identity were present many of the claims would have been rejected under 35 U.S.C. 102 as the structural limitations of most of the claims are so limited that virtually any prior art teaching of a structurally related nucleic acid would be encompassed. The absence of any such rejections is due

to the fact that the esterase encoded by SEQ ID NO:26 is substantially different than all prior art esterases.

Applicants argue that the Office appears to setting an erroneous standard that the specification must enable the skilled artisan to routinely identify every possible active variant of the exemplary sequence of the invention even though the proper legal test is that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. However, it is noted that the examiner has never required applicants to have taught the structure of every possible active variant but merely to limit the scope of the claims to a genus of possible variants for which randomly making variants and testing them for those retaining activity would not be undue experimentation to obtain a reasonable number of variants within the scope of the claims. However, applicants have repeatedly chosen not to do so. For all the reasons discussed above, the rejection for lack of enablement of the full scope of the invention is maintained.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3, 5, 40, 82, 98-102, 107-109, 110-111, 114-117, and 126 rejected under 35 U.S.C. 102(b) as being anticipated by Robertson et al. (WO 97/30160). The rejection was explained in the previous Office Action.

Applicants traverse the rejection by arguing that the priority claim to PCT/WO97/02039 has been perfected and thus Robertson et al. is not prior art. However, as noted previously, a renewed petition under 37 CFR 1.78(a)(3) or (a)(6) is necessary for the instant application to obtain the benefit of PCT/US07/02039. See the petition decision of 5/28/04. As such the rejection is maintained for the reasons of record, and is now applied to claims 40, 98-102, 109 as well in view of the amendments to make these claims dependent on claim 3 also.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Rebecca Prouty
Primary Examiner
Art Unit 1652

Continuation of Disposition of Claims: Claims pending in the application are 1-5,16,20-23,40-55,61-63,65,67,68,80-82,88-92,98-102,107-111,113-117 and 126.